patients requiring treatment for CLI (see also Critical Issue 2, p S34). The most commonly used generic instrument, the SF-36 questionnaire, has been used by some investigators in the evaluation of small groups of patients to determine whether its scale appropriately reflects the benefits of successful treatment. Functional status should be followed-up for at least 6 months postprocedure. Schneider and associates[5] used the SF-20, similar to the SF-36, a derivative of the Medical Outcomes Study, to evaluate 60 patients with CLI. This group noted that those with CLI had significant decreases in functional health and well-being despite successful revascularisation.

Duggan and colleagues[6] used the SF-36 questionnaire for the evaluation of 21 patients requiring treatment for CLI. Interestingly, they noted no significant difference in physical functioning between those patients with patent and those with failed bypasses. Additionally, the SF-36 did not indicate that patients with functioning bypasses had better emotional and general well-being scores. Chetter and associates[7] also employed the SF-36 to evaluate 235 patients, 78 of whom had CLI. They noted that the quality-of-life scores obtained through the SF-36 deteriorated as distal perfusion worsened. Thus, although there has been no broad standardisation of the SF-36 in patients with CLI, it represents the most obvious option at the present (see Recommendation 3, p S36).

Improvement in functional status

Improvement in functional status is often difficult to define in patients with CLI because of the presence of numerous and often severe comorbid conditions. Simple assessment of walking distance, though useful in some patients, does not apply to many. For example, those patients who have had a previous major amputation of the contralateral extremity may have an improved ability to pivot and transfer from bed to wheelchair after successful revascularisation of the contralateral leg. This improvement would not be detected by any current measures of functional status. Therefore, specific instruments capable of detecting improvement in functional status in this diverse patient population must be developed.

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D 4
TREATMENT OF CRITICAL LIMB ISCHAEMIA

D 4.1
Overall Strategy for Treatment of Critical Limb Ischaemia

Many of the principals of basic treatment discussed in relation to patients with intermittent claudication also apply to patients with CLI, although the urgency for rapid treatment of the latter group will alter the emphasis. For instance, the management of risk factors such as hyperlipidaemia is not of any immediate importance in patients with CLI. By contrast, other important aspects in the immediate basic treatment of patients with CLI, such as adequate control of pain, do not apply to claudication.

The principal urgent components of basic treatment of CLI are the control of pain and any infection in the ischaemic leg, prevention of progression of thrombosis if this is thought to be a precipitating factor in the ischaemia, and the optimisation of cardiac and respiratory function. While instituting basic treatment, the full precise morphology of the PAD should be simultaneously established by some form of imaging technique. This will determine further management of the arterial lesion. In a small group of patients, often delayed referrals, ischaemia and gross infection in the leg pose an immediate threat to the patient's survival. An immediate major amputation is mandatory and can be life saving in these cases, for instance, in a patient with gas or septic gangrene.

In most patients, the various options for endovascular techniques, arterial surgery, or thrombolysis can be carefully weighed. The primary aim is revascularisation to provide sufficient blood flow to relieve the rest pain and heal skin lesions. Most patients with CLI have multisegment arterial disease, and often the elimination of the most proximal obstruction might be sufficient to achieve these aims. It is, however, important to resist the temptation to only treat a relatively easy proximal lesion in the presence of extensive distal disease where the marginal improvement in blood flow may be insufficient to achieve healing. This applies especially where there has been tissue loss. For instance, angioplasty for relatively minor iliac stenosis is unlikely to achieve healing of a foot ulcer in the presence of extensive infrainguinal disease (see also D 4.2.2, p S165).

In general, if there is a balanced choice between an endovascular and a surgical procedure for a particular lesion, then the former is preferred because it usually avoids a general anaesthesia, poses a lesser systemic stress, and has fewer serious complications. However, the choice between an endovascular and a surgical procedure depends largely on the exact level and extent of the arterial disease; hence the need for a collaborative discussion of each case between endovascular and surgical specialists. For the same reason, in this section the optimal technique for revascularisation is discussed on an anatomic basis.

Having identified the best interventional techniques in a particular case, the risks and chances of success have to be weighed. There is no doubt that in some cases in which the risks of revascularisation are high and the chances of success low, there is a place for a primary major amputation or noninterventional therapy. Although a number of techniques are available for assessing the risks and benefit of a particular revascularisation procedure in a particular patient, they are still far from perfect. This is reflected by the number of patients who have an attempt at a series of revascularisation procedures that fail to achieve their purpose even in the short term and culminate in a major amputation.

There may be additional considerations in deciding whether to advise a patient to have a primary amputation. Not infrequently, patients with CLI will have other serious conditions limiting mobility, for instance, a neurological deficit from previous stroke. In fitter patients, it is necessary to estimate the chances of a patient fully mobilising on an artificial limb. There may be an argument for primary amputation in a patient who is likely to mobilise well on a prosthesis and in whom the chances of a successful revascularisation are slight.

More recently, available treatment options have been extended by the possibility of pharmacotherapy as a principal treatment. Published evidence so far only relates to the use of pharmacotherapy in patients with CLI who were unsuitable for any form of revascularization or in whom attempts at revascularisation have already failed. In these selected patients, pharmacotherapy may help to avoid or delay a major amputation and should be considered. The possibility of pharmacotherapy as a primary alternative to revascularization has not so far been studied. Its more established role is as an adjunct to either endovascular or surgical revascularization, where there is some evidence that adjunctive pharmacotherapy improves early and medium-term results at very little risk.

In summary, the management of a patient with CLI should proceed rapidly in conjunction with delineation of the arterial lesion. This is followed by a decision on the optimal form of revascularisation, which, if successful, will reverse the changes of CLI with minimum risk. If both surgery and endovascular techniques are equally feasible and likely to succeed initially and durably, the latter is preferred to surgery. The second decision is whether to apply this form of revascularisation or proceed to a primary amputation. Pharmacotherapy is a useful adjunct, but its role as primary treatment is not yet established.

D 4.2
Basic Treatment for Critical Limb Ischaemia

D 4.2.1
Control of Pain

A hallmark of CLI is ischaemic rest pain and painful ulceration. Aetiology of the pain is multifactorial, but it is primarily related to ischaemia of the skin in the distal extremity. Pain control is a critical aspect of the management of these patients. Ideally, relief of pain is achieved by reperfusion of the extremity. However, while setting up reperfusion, adequate pain control must be a goal of management in all patients. Furthermore, in patients for whom revascularisation is not possible, acetaminophen, nonsteroidal anti-inflammatory drugs, or narcotics may be necessary. Pain control should be individualised and multifactorial.

Physicians should assess pain severity and adequacy of pain relief in all patients at regular visits. Several pain scales are available, but simple scales that range from 0 to 10, with "0" indicating no pain and "10"indicating the most severe pain, are useful. Such scales

should be evaluated and recorded in the chart at each visit. Initial attempts at pain relief should include the use of acetaminophen or nonsteroidal antiinflammatory drugs. Caution should be used in the latter in patients with hypertension or renal insufficiency. Patients with severe unrelenting ischaemic pain also may require narcotics for adequate pain relief. Control of pain is usually more effective if analgesia is given regularly rather than on demand. In patients undergoing intervention, narcotics also may be required during the postoperative period. Placing the affected limb in the dependent position provides partial relief of ischaemic pain in some patients. Tilting the bed or use of a reclining chair therefore may be helpful measures in addition to analgesia.

Spinal cord stimulation has also been used in patients with inoperable severe lower extremity ischaemia (see also D 4.16.4, p S223). However, it currently cannot be recommended in patients with CLI. See Recommendation 82 (below). Epidural block is another effective form of pain control in various ABPI cases.

Recommendation 82: Pain control in critical limb ischaemia
Adequate treatment of ischaemic pain is mandatory in all patients with critical limb ischaemia and may require short-term use of narcotics. Pain control should be individualised and multifactorial. However, pain control treatment should not delay definitive treatment of the arterial lesion.

D 4.2.2
Foot Care in Patients With Critical Limb Ischaemia

Patients with chronic CLI must pay particular attention to proper foot care and avoid trauma to their extremities. These patients should be evaluated by a podiatrist and evaluated for proper foot care. Extremes of heat and cold should be avoided. Even mild physical trauma can convert a patient from having intact skin to an ischaemic ulcer. Thus, local measures are extremely important in the overall management of these patients (see also D 1.4, The Diabetic Foot, p S148).

D 4.2.3
Treatment of Life-Threatening Coexisting Disease

Patients with CLI are at the highest risk for subsequent myocardial infarction, stroke, and vascular death. Therefore, in addition to addressing the needs of their extremity, it is critical to reduce the systemic risk of mortality in this patient population. Many of these patients have impaired cardiac and renal function, sometimes having frank cardiac or renal failure. These coexisting conditions require active treatment by an expert in these areas. Improvement of cardiac output also will inevitably improve peripheral perfusion and go some way toward treating the CLI.

D 4.2.4
Treatment of Ulcers and Gangrene

Topical therapy

Several attempts have been made to improve topical therapy for ischaemic wounds in patients with CLI. This includes the use of topical antibiotics, growth factors, and debriding agents. These treatments are attractive and are often highly promoted by their sponsors. However, there are almost no controlled randomised trials to document the benefits of any topical agent to augment wound healing in this patient population. There may be substantial risk to the use of this therapy, because allergic reactions leading to dermatitis can be common with topical antibiotics.[1] Furthermore, reliance on topical therapy carries the risk of delaying reperfusion, and, except in neuropathic ulcers, topical agents are unlikely to be successful as the sole therapy. These agents are also expensive and often unnecessarily raise the expectation of the patient for a good result despite the absence of therapeutic efficacy.

Several novel dressings also have been proposed to treat these patients. These include hydrophilic dressings and seaweed. Most of the experience with these dressings has been in venous ulcers and not arterial ischaemic ulcers. Again, there are no data to support their use. Local treatment should aim to save as much skin tissue as possible; debridement should be avoided or kept at a minimum. Wet dressings, soaked in saline, can be used a few times a day to eliminate pus and tissue debris. Moist dressings also may be useful in reducing pain. Only once the ulcer has dried out should dry dressings be used. There is no indication for immobilising a patient with an ischaemic ulcer, unless the ulcer is on a weight-bearing area. A review of a few studies with becaplermin (rhPDGF-BB) gel suggests that ulcer healing may be improved.[2] The effectiveness of current topical agents—antibiotics, growth factors or hormones, debriding agents, or occlusive dressings—is not established.

Recommendation 83: Topical therapy for ischaemic ulceration
Topical therapy for ischaemic ulceration should be guided by the principles of wound care. The extremities should be kept clean, with appropriate debridement.

Systemic therapy

The use of systemic antibiotics may be indicated in patients with cellulitis. This is commonly seen in patients with diabetes with ischaemic wounds and may occur in any patient who converts from dry to wet gangrene, or who develops an infected ulcer. Signs and symptoms include swelling, redness, and tenderness at the site of infection. Bacteriology of these wounds is often polymicrobial, particularly in patients with diabetes. Therefore, signs of infection need to be aggressively treated. This often requires the use of systemic antibiotics to achieve adequate blood levels. Additional systemic agents for treating ischaemic wounds have not undergone rigorous trials. Anticoagulation is generally not warranted except in an attempt to maintain graft patency (see D 4.3.3, Pharmacotherapy Other Than Prostanoids, p S169, and D 4.13.3, Other Drugs, p S210). Antiplatelet therapy is useful as already described to reduce the systemic risk of cardiovascular disease (see Recommendation 28, p S871.

Recommendation 84: Systemic antibiotic therapy in patients with critical limb ischaemia
Systemic antibiotics are required in patients who develop cellulitis or spreading infection in ischaemic ulcers or gangrene but should not delay more definitive treatment.

D 4.2.5
Control of Risk Factors

Patients with CLI have the same cardiovascular risk factor profile as patients with claudication. However, patients with CLI have a more diffuse and extensive degree of atherosclerosis. Therefore, their risk of cardiovascular events and mortality is higher than that of patients with claudication. Despite the end-stage nature of this disease, aggressive systemic risk factor modification is still warranted.

Smoking cessation

The progression of peripheral arterial disease from asymptomatic to claudication to ischaemic rest pain is highly associated with cigarette smoking. In patients with severe disease, graft patencies are clearly improved by smoking cessation. This is true for both vein as well as prosthetic graft material. Amputation rates are also highly correlated with persistent cigarette smoking. In two series, the amputation rate was between 11% and 23% in those who continued to smoke, versus 0 to 10% in those who were smoking abstinent.[3] Finally, patient survival at 1, 3, and 5 years is also highly correlated with smoking. Therefore, in patients with severe end-stage disease, smoking cessation is still highly beneficial (see Recommendation 22, p S69).

Hypertension

Hypertension is a risk factor for all forms of cardiovascular disease. Although blood pressure elevations are a risk factor for peripheral arterial disease, maintaining an adequate blood pressure is important for limb perfusion. In patients with claudication, aggressive treatment of hypertension is associated with a modest reduction in treadmill exercise performance. In patients with severe chronic limb ischaemia, aggressive blood pressure treatment may decrease limb perfusion and thus result in worsening ischaemic rest pain or delayed healing of ischaemic ulcers.

Historically, patients with CLI have been treated by plasma volume expansion to increase blood pressure, thereby improving distal blood flow.[4] This therapy may be associated with temporary benefit but does expose the patient to the risk of stroke, congestive heart failure, and other untoward cardiovascular events. Therefore, inducing hypertension in this patient population is not recommended. Conversely, patients hospitalised for treatment of their severe leg ischaemia should not have their blood pressure acutely lowered unless there is evidence of active coronary ischaemia or congestive heart failure. Because there is the possibility of vasoconstriction with beta-blocker antihypertensive agents, their use in CLI should be carefully considered. When such antihypertensives are used, CLI patients should be monitored for worsening of ischaemic ulcers.

Diabetes

Diabetes is an important risk factor for all forms of peripheral arterial disease and also greatly contributes to CLI (see A 2, Epidemiology, Natural History, Risk Factors, p S4). In addition to the risk of atherosclerotic arterial occlusive disease, patients with diabetes also develop neuropathy, which increases the risk for

developing nonhealing neurotrophic ulcers. In addition to the neuropathy, hyperglycaemia will inhibit white cell function, thus predisposing the patient to infection (see also D 1.4, Diabetic Foot p S148). A comprehensive approach to treating patients with diabetes would include proper footwear, with attention to areas of trauma from poorly fitting shoes (see D 4.2.2, Foot Care, p S165). Patients with nonhealing ulcers often need to be treated in the hospital to provide comprehensive management, including wound care and eventually systemic antibiotics. In addition, aggressive control of blood sugar is warranted in these patients, with an attempt to maintain fasting blood sugars below 120 mg/dL and postprandial sugars less than 180 mg/dL. Chronic management should attempt to normalise glycohaemoglobin levels to less than 7.0% (see Recommendation 23, p S69).

Hyperlipidaemia

The lipid risk profile for patients with peripheral arterial disease is similar between those with claudication and those with CLI. There are no data regarding recommendations in the severe leg ischaemia patient population. However, extrapolation from patients with intermittent claudication as well as from the National Cholesterol Education Program Guidelines would recommend aggressive treatment of LDL cholesterol levels and attempts to raise the HDL cholesterol and lower triglyceride levels. Therefore, patients with CLI should have an LDL cholesterol level maintained at 100 mg/dL or less (see Recommendation 25, p S70). The goals of therapy are to reduce the systemic risk of myocardial infarction and cardiovascular death, as well as to delay the progression of peripheral atherosclerosis.

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D 4.3
Pharmacotherapy for Critical Limb Ischaemia

D 4.3.1
Introduction

For decades, pharmaceutical and clinical research aimed at improving the morbidity of claudication has centred around vasodilators. Direct-acting vasodilators can increase blood flow in normal resting skeletal muscle. However, it is unlikely that any vasodilator can significantly increase blood flow distal to a physical occlusion. Autoregulatory mechanisms in skeletal muscle beds produce dilation in response to ischaemia; hence, vasodilators will increase blood flow primarily to non-ischaemic areas. The concept of vasodilatation has moved to vasoreactive or vasorecruiting drugs and more recently to agents improving unbalanced or compromised microcirculation distal to an arterial obstruction. Another approach is to search for compounds that improve the blood rheology. The use of thrombolytic drugs in CLI is also to be considered, most often to be followed by endovascular or surgical treatment.

The ideal treatment for critical limb ischaemia must be the elimination or bypass of the occlusions in the larger arteries, but this is often impossible or else it fails. An alternative in these cases is to try to modify the consequences of the low perfusion pressure on the distal microcirculation sufficiently by some form of pharmacotherapy to reverse the rest pain and avoid amputation.

Pharmacological management of CLI must be based on an improved understanding of its pathophysiology. The main components, lack of autoregulation of the microvascular flow-regulating system and inappropriate activation of the microvascular defence system, are both thought to be significantly regulated by prostacyclin.[1] Breakdown of the microvascular flow-regulating system is manifested in particular by abnormal vasomotion and a maldistribution of blood flow away from the nutritive skin capillaries. Activation of the microvascular defence system results in interacting activation of white blood cells, platelets, and the damaged endothelium. The resultant capillary obstruction, increased capillary permeability, tissue oedema, and the liberation of activated products of leukocytes, such as oxygen free radicals, platelet-activating factor, and proteolytic enzymes, leads to a vicious cycle with further capillary obstruction.

D 4.3.2
Prostanoids

Prostanoids have been shown to have beneficial effects on most of the microcirculatory components by